Pharmacodynamic activity and clinical benefits of mezigdomide in high-risk biomarker subgroups from the CC-92480-MM-001 study

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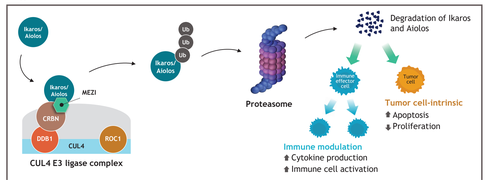
Introduction

- Mezigdomide (MEZI) is an oral CELMoD™ agent that induces maximal and rapid degradation of Ikaros and Aiolos compared with immunomodulatory drug (IMiD®) agents. Reduction in these transcription factors results in direct tumoricidal and immunomodulatory effects in multiple myeloma (MM) **(Figure 1)**[1-4]
- MEZI showed promising efficacy and safety in combination with dexamethasone (DEX) in the phase 1/2 CC-92480-MM-001 trial (NCT03374085) in relapsed/refractory MM (RRMM)[5,6]
- The effects of MEZI in high-risk molecular subgroups and/or plasmacytoma refractory to multiple prior therapies are unclear
- A biomarker plan was developed based on mechanistic understanding of MEZI to better understand the pharmacodynamic (PD) activities in high-risk subgroups, and the potential associations of biomarker changes with clinical activity to support dose selection in combination strategies for MEZI

Figure 1. MEZI mechanism of action



CRBN, cereblon; CUL4, cullin 4; DDB1, DNA damage-binding protein 1; ROC1, regulator of cullins-1; Ub, ubiquitin.

Objective

- To report biomarker analyses to better understand PD and clinical activity of MEZI in high-risk biomarker subgroups

Methods

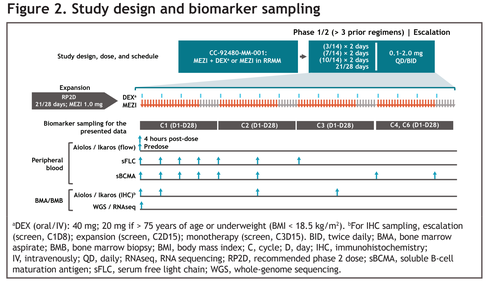
Study design

- CC-92480-MM-001 is a phase 1/2 trial evaluating MEZI monotherapy or in combination with DEX (MEZI-d) in patients with RRMM, with doses ranging from 0.1 to 2.0 mg across multiple dosing schedules[6] **(Figure 2)**
- Key eligibility criteria:
  - Patients in part 1 had received ≥ 3 prior lines of antimyeloma therapy, including ≥ 2 consecutive cycles of lenalidomide (LEN), pomalidomide (POM), a proteasome inhibitor (PI), an anti-CD38 monoclonal antibody (mAb), and a glucocorticoid
  - Part 2 included the criteria above and refractoriness to LEN and/or POM, a PI, an anti-CD38 mAb, and a glucocorticoid

Translational analyses

- Clinical biomarkers were analyzed in peripheral blood and bone marrow samples **(Figure 2)**
  - Peripheral blood samples were collected on treatment C1D1 pre- and post-dose to assess Aiolos expression in T cells; sFLCs and sBCMA were analyzed as tumor burden biomarkers from C1 to C6
  - Bone marrow samples were collected for IHC at screening through mid-C3, and for genomics analyses at screening

Figure 2. Study design and biomarker sampling



[a]DEX (oral/IV): 40 mg; 20 mg if > 75 years of age or underweight (BMI < 18.5 kg/m²). [b]For IHC sampling, escalation (screen, C1D8); expansion (screen, C2D15); monotherapy (screen, C3D15). BID, twice daily; BMA, bone marrow aspirate; BMB, bone marrow biopsy; BMI, body mass index; C, cycle; D, day; IHC, immunohistochemistry; IV, intravenously; QD, daily; RNAseq, RNA sequencing; RP2D, recommended phase 2 dose; sBCMA, soluble B-cell maturation antigen; sFLC, serum free light chain; WGS, whole-genome sequencing.

Results

- Baseline characteristics of patients are presented in **Table 1**

Table 1. Patient baseline characteristics

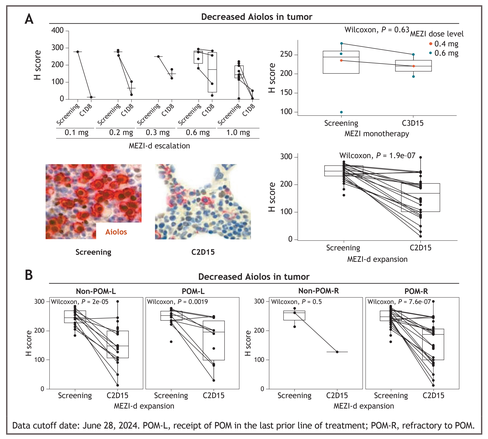
Characteristic	Monotherapy cohort (n = 17)	Dose-escalation cohort (n = 77)	Dose-expansion cohort (n = 101)
Age, median (range), years	69 (50-76)	65 (40-78)	67 (42-85)
Male, n (%)	9 (53)	45 (58)	55 (55)
Race, n (%)			
White	15 (88)	69 (90)	77 (76)
Black	0	3 (4)	4 (4)
Asian	1 (6)	1 (1)	7 (7)
Other/not reported	1 (6)	4 (5)	13 (13)
Time since initial diagnosis, median (range), years	8.4 (4.2-13.2)	7.3 (0.9-23.3)	7.5 (1.1-37.1)
Presence of plasmacytoma, n (%)	6 (35)	27 (35)	40 (40)
Number of previous lines of therapy, median (range)	5 (2-7)	4.5 (1-13)	6 (3-15)
Previous therapy, n (%)			
Stem cell transplantation	12 (70.6)	60 (78)	78 (77)
PI	17 (100)	77 (100)	101 (100)
LEN	17 (100)	76 (99)	101 (100)
POM	17 (100)	71 (92)	101 (100)
Anti-CD38 mAb	17 (100)	60 (78)	101 (100)
Anti-BCMA antibody	4 (23.5)	9 (12)	30 (30)
ADC	1 (5.9)	7 (9)	22 (22)
TCE	2 (11.8)	1 (1)	8 (8)
CAR T cell	1 (5.9)	1 (1)	3 (3)
Triple-class refractory, n (%)	14 (82)	42 (54.5)	97[a] (96)

Data cutoff date: June 28, 2024. [a]For each prior anti-MM treatment, the treatment start/stop date was collected. If month or year of the date was missing, date would not be imputed and treated as missing. ADC, antibody-drug conjugate; CAR, chimeric antigen receptor; TCE, T-cell engager.

Aiolos degradation in tumors

- Patients who received MEZI-d or MEZI monotherapy showed Aiolos degradation across all doses tested **(Figure 3A)**
- In patients who were POM-L and/or POM-R, MEZI-d was able to induce Aiolos degradation **(Figure 3B)**

Figure 3. MEZI-d induced Aiolos degradation in tumors across all doses tested and independent of POM-L/POM-R

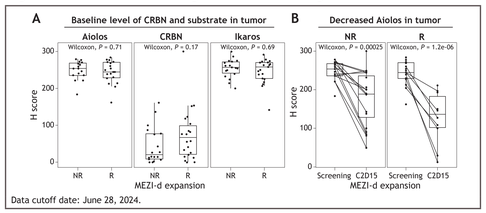


Data cutoff date: June 28, 2024. POM-L, receipt of POM in the last prior line of treatment; POM-R, refractory to POM.

Baseline and PD activity in responders (R) and nonresponders (NR)

- Comparable baseline expression of Ikaros and Aiolos was observed in R (defined as partial response or better) and NR **(Figure 4A)**
  - While there was a trend of lower baseline expression of CRBN in NR, it was not significant
  - Low baseline CRBN expression was also observed in some R
- MEZI-d induced Aiolos degradation in R and NR **(Figure 4B)**

Figure 4. Baseline and changes in substrate degradation in R and NR

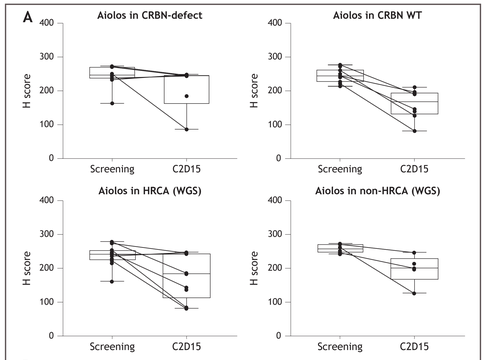


Data cutoff date: June 28, 2024.

PD and clinical activity in tumors

- MEZI-d induced Aiolos degradation in tumors of patients with CRBN-defect or ≥ 1 high-risk cytogenetic abnormality (HRCA) **(Figure 5A)**
- WGS showed that MEZI-d induced clinical response in some patients with ≥ 1 CRBN-defect and/or ≥ 2 HRCAs **(Figure 5B)**

Figure 5. MEZI-d showed PD and clinical activity in some patients with CRBN-defect and HRCA

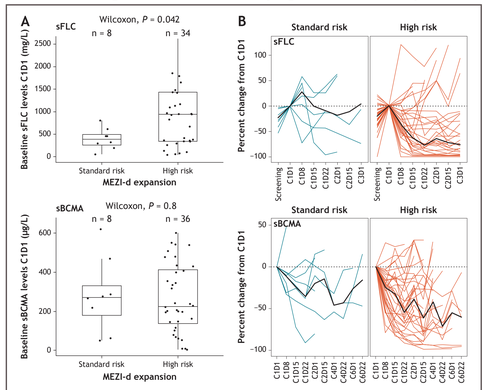


Data cutoff date: June 28, 2024. Tan arrows indicate CRBN-defect or HRCA in R, as follows: CRBN-defect: CRBN LOH, and/or COPS7Bdel, and/or COPS8del, and/or del10, and/or CRBN mutation; HRCA (WGS): del17p, and/or TP53, and/or t(4:14), and/or t(14:16), and/or amp1q, and/or del1p. A: MEZI-d expansion. B: MEZI-d (escalation and expansion), MEZI monotherapy. CNV, copy number variation; LOH, loss of heterozygosity; NA, not available; WT, wild type.

Baseline and changes in tumor burden biomarkers in patients with HRCA or plasmacytoma

- Patients with HRCA showed higher baseline sFLCs than standard-risk patients (P = 0.042; with limited n), but comparable baseline sBCMA **(Figure 6A)**, and reduced sFLCs and sBCMA with MEZI-d treatment **(Figure 6B)**
  - Response was reported in 12 of 37 high-risk patients (32.4%) versus 2 of 8 standard-risk patients (25.0%)

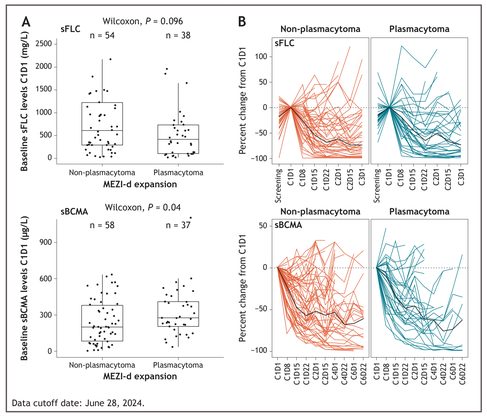
Figure 6. Baseline and changes in tumor burden biomarkers in patients with high or standard risk of cytogenetic abnormality



Data cutoff date: June 28, 2024. High risk (IHC): del(17p), and/or t(4;14), and/or t(14;16), and/or 1q21Amp.

- Patients with plasmacytoma showed slightly higher baseline sBCMA than non-plasmacytoma patients (P = 0.04; with limited n), but comparable baseline sFLCs **(Figure 7A)**, and reduced sFLCs and sBCMA with MEZI-d treatment **(Figure 7B)**
  - Response was reported in 12 of 40 patients with plasmacytoma (30.0%) versus 28 of 59 patients without plasmacytoma (47.5%)

Figure 7. Baseline and changes in tumor burden biomarkers in patients with or without plasmacytoma



Data cutoff date: June 28, 2024.

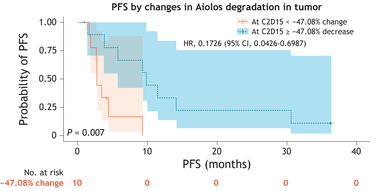
Association of biomarker changes with clinical activity

- Aiolos degradation in tumor, but not blood, was significantly associated with improved progression-free survival (PFS) in patients treated with MEZI-d by Cox proportional hazards (CoxPH) regression model (P = 0.006) **(Figure 8A)**
- Kaplan-Meier (KM) survival analysis using the median as the cut point showed a significant improvement in PFS for patients who had Aiolos degradation ≥ −47.1% (median PFS [mPFS] 9.9 months) compared with those with Aiolos degradation < −47.1% (mPFS 2.8 months) (log rank, P = 0.007)
- Patients who had a greater decrease in their involved light chain during the first 3 cycles of treatment also had a significant improvement in PFS (CoxPH, P < 0.000001) **(Figure 8B)**
- KM analysis showed that PFS was significantly longer for patients achieving a nadir sFLC reduction of ≥ −78.6% (mPFS, 7.1 months) compared with those with sFLCs < −78.6% (mPFS, 2.3 months) (log rank, P < 0.001)

Figure 8. Association of changes in biomarkers with clinical response

A

Sample	CoxPH model	N[a]	N with event[b]	HR[c] (95% CI)	P value
Blood (Aiolos in T cell)	PFS~C1D1-4HR (%)	72	58	1.002 (0.985-1.019)	0.837
Tumor (Aiolos)	PFS~C2D15 (% change)	19	16	1.035 (1.01-1.06)	0.006



B

CoxPH model	N[a]	N with event[b]	HR[c] (95% CI)	P value
PFS~Nadir C1D8-C3D1 sFLC	92	71	1.0140 (1.0088-1.0193)	1.32e-07

Data cutoff date: June 28, 2024. Cohort: 1.0 mg MEZI-d 21/28. [a]Total patients; [b]Number of patients who experienced an event (progression/death); [c]HR reported by CoxPH corresponds to 1 unit increase in % change. CI, confidence interval; HR, hazard ratio.

Conclusions

- MEZI-d was pharmacodynamically active in patients across all doses tested and in patients who received POM in the last prior line of treatment and/or were refractory to POM, and showed clinical response regardless of baseline CRBN expression levels
- MEZI-d showed PD activities, reduced tumor burden biomarkers, and resulted in clinical response in patients with CRBN-defect and/or HRCA, suggesting MEZI-d may be a relevant option to improve outcomes for patients with RRMM and high-risk molecular features
- Early changes in biomarkers (within the first 3 cycles) were associated with long-term clinical activity and supported the use of combination strategies for MEZI
  - These included potent, deep Aiolos degradation in tumors and reductions in involved light chain
- Validation of these biomarker analyses in high-risk molecular subgroups and association of early changes with response are being investigated in phase 3 trials in patients with RRMM: SUCCESSOR-1 (MeziVd vs PomVd) and SUCCESSOR-2 (MeziKd vs Kd)

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